

Qual Life Res (2010) 19:1285–1293
DOI 10.1007/s11136-010-9699-0

Patient treatment satisfaction after switching to NovoMix[®] 30 (BIAsp 30) in the IMPROVE[™] study: an analysis of the influence of prior and current treatment factors

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Accepted: 15 June 2010 / Published online: 4 July 2010

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Abstract

Purpose Understanding treatment satisfaction (TS) for diabetes is increasingly important as treatment options increase. This study examines treatment satisfaction with NovoMix[®] 30 in an observational study in patients with type 2 diabetes.

Methods The DiabMedSat assesses Overall, Treatment Burden, Symptom and Efficacy Treatment Satisfaction. The impact of type of pretreatment variables on TS was examined by ANOVA at baseline and week 26. Satisfaction at week 26 was examined by *t*-test and effect size. Linear regression models examined impact of prior treatment factors (age, gender, duration of diabetes, type of prior treatment and diabetes-related comorbidities) and current treatment factors (weight gain, hypoglycemic events, reaching therapeutic goal) on TS.

Results The data set comprised 17,488 persons. Prior treatment with insulin had a more positive impact on baseline satisfaction. At week 26, there were no differences between type of prior treatment groups in Overall, Symptoms and Burden TS. Current treatment with NovoMix 30 significantly improved TS. Regression analyses examining the combined effect of pretreatment factors and current treatment factors found that all factors except for age-impacted TS although the domains impacted varied.

Conclusions Patients treated with NovoMix 30 reported improved treatment satisfaction, and the improvement is considered clinically meaningful to patients.

Keywords Treatment satisfaction · Observational study · Diabetes mellitus

Abbreviations

BMI	Body mass index
Insulin + OAD	Those taking insulin along with an oral treatment
PRO	Patient-reported outcome
TS	Treatment satisfaction

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Background

Understanding treatment satisfaction for diabetes is especially important given the ever increasing range of treatment options for patients with diabetes. Treatment satisfaction (TS) is a key patient-reported outcome (PRO) as it has been found to impact patient compliance [1, 2], cost of care [3, 4] and self-management behaviors [5], as well as significantly differ between drug treatment options [6, 7]. The treatment

for approximately 30% of patients with diabetes in US is insulin [8], the most potent drug available to achieve glycemic targets [9]. Unfortunately, insulin use often involves negative perceptions and may present an emotional and logistical hurdle leading to patient resistance to treatment [10–12], and it has been found that, when examining the willingness of type 2 insulin-naïve diabetic patients to begin insulin, negative attitudes toward insulin are common [13]. Persons with diabetes who perceive injecting insulin as burdensome may experience more negative health outcomes [14], whereas patients who are satisfied with their treatments are more likely to maintain positive physical and psychological health [15].

Unfortunately, patient characteristics such as age and gender as well as treatment outcomes such as the experience of side effects, which may differentially influence treatment satisfaction depending upon the stage of treatment (treatment initiation vs. during treatment), are not well understood [16]. Studies have reported that treatment satisfaction may be positively or negatively associated with age [17–20]. Duration of diabetes has been shown to predict poorer quality of life and poorer glycemic control [21, 22]. Several studies have observed an association between treatment satisfaction and type of treatment (e.g., insulin vs. oral, type of insulin delivery device) [7, 23–30], and overall treatment satisfaction has been shown to be significantly improved after switching treatment from orals or orals with insulin to treatment with Biphasic Insulin Aspart 30 [31]. At least three studies reported reduced treatment satisfaction among women [23, 32, 33]. Diabetes-related comorbidities such as neuropathy have been found to predict decreased treatment satisfaction [16, 23, 32, 33].

Previous research has also shown that concerns with treatment side effects, especially hypoglycemia and weight gain, can negatively affect patient perceptions of insulin therapy and lead to diminished treatment efficacy. Fear of weight gain may increase a patient's psychological and treatment burden, diminishing treatment satisfaction [34, 35]. Two studies found that approximately 1/3 of female subjects with type 1 diabetes omitted insulin in order to control their weight [36, 37]. Since weight gain is further associated with insulin resistance, it may also compromise treatment efficacy [38]. Experiencing hypoglycemic events has been associated with lower levels of treatment satisfaction [33, 39], while patients fearful of hypoglycemia have been reported to limit their blood glucose control regimen in order to avoid triggering a hypoglycemic event [34].

Thus, to more accurately characterize the impact of patient/disease characteristics and treatment outcomes on treatment satisfaction, a more comprehensive approach examining potentially relevant pretreatment (e.g., age) and during treatment (e.g., side effects) variables is necessary

to fully understand factors that exert an influence on shaping treatment satisfaction with treatment in diabetes.

The IMPROVE study is a multicenter, 26-week, open-labeled, non-randomized and non-interventional observational study of the safety and efficacy of Biphasic Insulin Aspart 30 (NovoMix 30) for the treatment of diabetes in routine practice patients with type 2 diabetes [31]. The DiabMedSat was included in the IMPROVE study as it is used to examine the impact of treatment on patient-reported treatment satisfaction, and it is a well validated disease-specific PRO measure designed to assess treatment satisfaction both in persons with type 1 or type 2 diabetes and across multiple treatment modalities (oral, syringe, pen) [40, 41]. This study further examines treatment satisfaction in the IMPROVE study by exploring the influence of the pretreatment factors (age, gender, duration of diabetes, type of prior treatment and diabetes-related comorbidities) and the impact of treatment side effects (weight gain, hypoglycemic events) on both overall treatment satisfaction and on the individual domains of treatment side effects, burden and efficacy in diabetes.

Methods

Eligible patients for the analyses presented here were any with type 2 diabetes who needed insulin treatment at the time of inclusion including newly diagnosed patients. Analyses were conducted with all patients who had DiabMedSat data at both baseline and week 26 (end of study treatment) and had been on an identifiable diabetes treatment prior to entering the IMPROVE study. Patients treated only with diet/exercise at baseline were dropped from the analysis and did therefore not complete the questionnaire at baseline.

The 22-item DiabMedSat assesses three treatment satisfaction domains of Efficacy, Treatment Burden and Symptoms (Side Effects) and Overall treatment satisfaction and has been translated into multiple languages according to well-established principles of translation [42]. The measure has been shown to have acceptable reliability, validity and responsiveness [41] in patients with diabetes similar to those enrolled in IMPROVE study [16, 41]. Valid DiabMedSat observations were obtained from seven countries in the IMPROVE study (Canada, China, India, Italy, Japan, Poland and Russia) and were part of the same data set as reported by Valensi et al. [31].

All statistical tests were two-tailed and conducted with an alpha level of 0.05 as minimal threshold for significance. As the DiabMedSat is intended to be used either as a total score or as independent domains, the testing was conducted for both the total and domain scores. The scope of this analysis was aimed at the assessment of treatment

satisfaction regardless of cultural differences; hence, the analyses were conducted on the pooled sample. All analyses conducted were based on an a priori statistical analysis plan (SAP).

Prior treatment factors

Key patient and diabetes-related factors (age, gender, duration of diabetes, prior treatment and diabetic-related comorbidities) that were assessed at baseline and thus existed before treatment start were classified as prior treatment factors. First, the impact of type of pretreatment (defined as orals only, insulin only and insulin plus orals) on TS was examined by comparing the means (ANOVA) of each DiabMedSat domain and overall scores at baseline, week 26 and the change between baseline and week 26 by each pretreatment group. The baseline DiabMedSat assessed treatment satisfaction with treatments prior to the IMPROVE study. Linear regression models, one for each domain and overall score, were then conducted to examine the impact that the key prior treatment factors (age, gender, duration of diabetes, prior treatment, and diabetic-related comorbidities) had on current satisfaction when examined together.

An exploratory chi-square was performed to examine, on an item level, change from baseline to end of study by pre-study treatment therapy (insulin + OAD, OAD only).

Current treatment factors

To assess treatment satisfaction with current treatment (Biphasic Insulin Aspart 30 (NovoMix 30)), change scores between baseline and week 26 were examined by paired *t*-test comparison and by effect size.

Linear regression models were then conducted to examine the impact of key current treatment factors (weight gain in kg, hypoglycemic events, achievement of physician-determined HbA1c goal and study treatment group) on treatment satisfaction when examined together.

A final regression analysis examined the combined impact of all previously identified significant pretreatment and current treatment factors on treatment satisfaction when examined together.

Results

The total IMPROVE data set comprised 19,824 people with type 2 diabetes: 6 were dropped due to incomplete demographics (no age or gender); 1,031 were dropped for not completing the DiabMedSat measure; and 1,299 were dropped due to lack of information on prior treatment. Thus, the analytic data set for the analyses reported here was

comprised of 17,488 persons. The average age of the sample was 57.2 years, with a baseline body mass index (BMI) of 26.2 kg/m² and most recent HbA1c of 9.2%. The mean length of time with diabetes was 6.9 years. Most of the sub-sample (90.4%) were on oral treatments alone before starting the study; the rest of the sample were on insulin with or without oral treatment. The most common reasons physicians reported for starting patients on treatment were related to improving treatment efficacy (HbA1c, fasting glucose, post-prandial blood glucose) or patient treatment satisfaction. Patients who were dropped were significantly ($P < 0.001$) older (mean age 62.1 vs. 57.2), had a longer duration of diabetes (mean of 13.9 vs. 6.9 years), a lower HbA1c (mean 8.8 vs. 9.2) and a higher BMI (mean 31.6 vs. 26.2) than those in the analytic data set (Table 1).

Prior treatment factors

The impact of type of prior treatment showed that at baseline greater levels of TS (overall and the three domains) were seen in the cohort using insulin alone. Baseline satisfaction was slightly lower in those taking insulin along with an oral treatment (Insulin + OAD).

At week 26 of the study, patients previously on Insulin + OAD had a greater satisfaction with treatment efficacy compared to patients on orals alone. There were no differences between type of prior treatment groups in DiabMedSat Overall scores and for the Symptoms and Burden domains.

When examining the change in satisfaction from baseline to week 26, larger changes were seen in the overall, as well as in every domain, for patients who were previously on an oral treatment either alone or in combination with insulin (Table 2).

Regression analyses examining the combined effect of pretreatment factors (age, gender, duration of diabetes, prior treatment and diabetic-related comorbidities) found that greater age was significantly associated with increased levels of Overall satisfaction and for the Efficacy, and Burden domains of the DiabMedSat. Those patients having diabetes for a longer duration were significantly associated with greater levels of satisfaction with the Burden domain. Subjects on insulin only (pre-study) showed significantly greater levels of satisfaction with the Overall, Efficacy and Symptoms domains of the DiabMedSat. Having diabetes-related comorbidities before entering the study were significantly associated with greater satisfaction with the Symptoms domain and lower levels of satisfaction in the Burden domain (Table 3).

The exploratory chi-square analysis of item level change from baseline to end of study by pre-study treatment revealed that the proportion of patients who were “very or extremely satisfied” (highest improvements on scale)

Table 1 Demographics data: DiabMedSat sub-sample ($n = 17,488$)

Country	
<i>N</i> (%) Canada	438 (2.5%)
<i>N</i> (%) China	12,758 (73.0%)
<i>N</i> (%) India	349 (2.0%)
<i>N</i> (%) Italy	33 (0.2%)
<i>N</i> (%) Japan	144 (0.8%)
<i>N</i> (%) Poland	3,186 (18.2%)
<i>N</i> (%) Russia	580 (3.3%)
Age	
Mean (SD) ($n = 17,486$)	57.2 (12.0) Range 8–99
Gender	
<i>N</i> (%) Male	9,904 (56.6%)
<i>N</i> (%) Female	7,584 (43.4%)
Body mass index (BMI)	
Mean (SD) baseline ($n = 17,483$)	26.2 (4.8) Range 12.8–66.6
HbA1c	
Mean (SD) most recent ($n = 12,981$)	9.2 (1.9) Range 4–16
Diabetes duration (years)	
Mean (SD) ($n = 17,481$)	6.9 (5.2) Range 0–42
No. of diabetes-related complications	
Mean (SD) baseline ($n = 14,302$)	0.6 (0.5) Range 0–1
Pre-study therapy	
<i>N</i> (%) OAD (oral anti-diabetics) only	15,816 (90.4%)
<i>N</i> (%) insulin only	961 (5.5%)
<i>N</i> (%) insulin + OAD	711 (4.1%)
Reasons for starting NovoMix 30 ^a	
<i>N</i> (%) easy start of therapy	11,388 (65.1%)
<i>N</i> (%) easy identification of insulin therapy	8,673 (49.6%)
<i>N</i> (%) to improve HbA1c	13,907 (79.5%)
<i>N</i> (%) to improve FBG	14,094 (80.6%)
<i>N</i> (%) to improve PPBG	13,524 (77.3%)
<i>N</i> (%) reduce risk of hypoglycemia	7,138 (40.8%)
<i>N</i> (%) patient dissatisfaction with previous therapy	9,238 (52.8%)
<i>N</i> (%) side effects from previous therapy	3,798 (21.7%)
<i>N</i> (%) change due to insulin pen	1,253 (7.2%)
<i>N</i> (%) allow for mealtime administration	7,610 (43.5%)

^a Not mutually exclusive categories

increased significantly from baseline to end of study particularly on questions related to ‘reduce tiredness’, ‘control blood sugar’ and ‘reduce worries about complications’. For patients previously on Insulin \pm OADs, these questions, respectively, increased from 12.4, 11.4 and 13.9% at baseline to 47.6, 49.1 and 39.3% after 26 weeks. For patients previously on OADs alone, these questions, respectively, increased from 7.5, 6.9 and 9.3% at baseline to 50.1, 49.7 and 35% after 26 weeks.

Current treatment factors

Examining the impact of current treatment with Biphasic Insulin Aspart 30 (NovoMix 30) found that treatment

satisfaction significantly ($P < 0.001$) improved with treatment. Change scores ranged from 11.0 points (Symptoms domain) to 28.7 points (Efficacy domain). Effect size calculations were moderate to high ranging from 0.55 (Symptoms domain) to 1.69 (Efficacy domain) (Table 4).

A regression analysis examining the impact of experiencing treatment side effects (weight gain, minor hypoglycemic events) and patient achievement of physician-determined HbA1c found that weight gain and experiencing minor hypoglycemic events were negatively associated with satisfaction in each of the DiabMedSat domains as well as the total score. Achievement of HbA1c levels was associated with greater satisfaction in Symptoms and Burden domains. Correlations between the DiabMedSat domains

Table 2 Impact of prior treatment (baseline, week 26 and change)

		1	2	3	
		OAD only	Insulin only	Insulin + OAD	Sig. ^a
Baseline					
DiabMedSat: efficacy	Mean	42.3 (16.8)	48.9 (16.5)	45.1 (19.7)	.000
	<i>N</i>	15,624	947	707	
DiabMedSat: symptoms	Mean	64.2 (20.3)	67.6 (18.9)	63.2 (20.3)	.000 ^b
	<i>N</i>	15,661	950	700	
DiabMedSat: burden	Mean	63.6 (14.4)	63.9 (13.4)	59.2 (14.6)	.000 ^c
	<i>N</i>	15,507	935	698	
DiabMedSat: overall	Mean	56.6 (13.1)	60.1 (12.8)	55.7 (14.5)	.000 ^d
	<i>N</i>	15,816	961	711	
Week 26					
DiabMedSat: efficacy	Mean	71.3 (15.2)	72.3 (13.7)	73.3 (14.7)	.001 ^e
	<i>N</i>	15,666	954	703	
DiabMedSat: symptoms	Mean	75.2 (15.8)	76.0 (14.1)	76.0 (14.3)	.148
	<i>N</i>	15,678	955	698	
DiabMedSat: burden	Mean	75.7 (14.1)	75.9 (14.2)	75.1 (14.1)	.554
	<i>N</i>	15,549	951	691	
DiabMedSat: overall	Mean	74.0 (11.9)	74.8 (11.2)	74.8 (11.4)	.067
	<i>N</i>	15,797	961	710	
Change					
DiabMedSat: efficacy	Mean	29.0 (22.0)	23.4 (19.7)	28.4 (23.8)	.000 ^f
	<i>N</i>	15,479	940	699	
DiabMedSat: symptoms	Mean	11.1 (21.0)	8.3 (19.4)	13.1 (21.3)	.000
	<i>N</i>	15,525	944	688	
DiabMedSat: burden	Mean	12.2 (18.0)	12.0 (17.5)	16.0 (18.9)	.000 ^g
	<i>N</i>	15,249	925	679	
DiabMedSat: overall	Mean	17.4 (16.0)	14.6 (14.7)	19.1 (17.3)	.000
	<i>N</i>	15,797	961	710	

^a Analysis of variance (ANOVA)^b Using ANOVA contrasts: column 1 and 3 are not significant ($P = 0.199$)^c Using ANOVA contrasts: column 1 and 2 are not significant ($P = 0.452$)^d Using ANOVA contrasts: column 1 and 3 are not significant ($P = 0.092$)^e Using ANOVA contrasts: column 2 and 3 are not significant ($P = 0.120$)^f Using ANOVA contrasts: column 1 and 3 are not significant ($P = 0.479$)^g Using ANOVA contrasts: column 1 and 2 are not significant ($P = 0.710$)

and minor hypoglycemic episodes and weight gain were small (0.007–0.055) minimizing the potential multicollinearity in the regression models (Table 5).

A final regression analysis examined the combined significant predictors from both the pretreatment and the current treatment analyses. No differences were found when all pretreatment and during treatment factors were examined in combination as when the pretreatment and during treatment variables were examined separately with the exceptions that age dropped significance in Efficacy and reaching the physicians HbA1c goal dropped significance in the Symptom domain.

Discussion

Treatment satisfaction is an important factor in determining the success of treatment in diabetes. This study found that patients who were treated with Biphasic Insulin Aspart 30 (NovoMix 30) reported improved treatment satisfaction after 26 weeks of treatment and that the improvement in treatment satisfaction is large enough to be considered clinically meaningful to patients.

Treatment satisfaction is a complex concept encompassing not only satisfaction with treatment efficacy but also the burden and side effects of treatment [40]. Additionally, as

Table 3 Impact of pre-study variables on satisfaction

Pre-study variables	DiabMedSat (week 26) (coefficient, <i>t</i> -ratio)			
	Overall***	Efficacy**	Symptoms***	Burden***
Intercept	72.520 (132.5)***	70.973 (101.7)***	74.004 (105.4)***	72.828 (111.1)***
Age (years)	0.034 (3.8)***	0.032 (2.8)**	0.020 (1.7)	0.047 (4.3)***
Gender (Female = 1)	0.254 (1.2)	.291 (1.1)	0.249 (1.0)	0.267 (1.1)
Diabetes duration (years)	0.016 (0.7)	−0.033 (−1.2)	0.009 (0.3)	0.070 (2.7)**
Prior treatment (1 = OAD only) (0 = insulin only)	−1.171 (−3.8)***	−1.124 (−2.8)**	−2.382 (−6.0)***	0.043 (0.1)
Diabetic-related comorbidities (before study) (1 = Yes)	0.188 (0.9)	0.092 (0.3)	1.204 (4.3)***	−0.670 (−2.6)*
<i>F</i> -stat ^a	8.410***	3.678**	14.153***	8.275***

* $P < 0.05$; ** $P < 0.01$, *** $P < 0.001$

^a The *F*-statistic is a hypothesis test that all variables as a group in the model significantly affect the dependent variable

Table 4 Impact of current treatment (NovoMix 30) on satisfaction

Total sample	<i>n</i>	Baseline mean (SD)	Week 26 mean (SD)	Change score mean (SD)	<i>t</i> -Stat (sig.)	Effect size ^a
DiabMedSat						
Efficacy	17,118	42.8 (16.9)	71.5 (15.1)	28.7 (21.9)	171.0 (.000)	1.698
Symptoms	17,157	64.3 (20.2)	75.3 (15.6)	11.0 (20.9)	68.9 (.000)	0.545
Burden	16,853	63.4 (14.3)	75.7 (14.1)	12.4 (18.0)	88.9 (.000)	0.867
Total	17,468	56.7 (13.2)	74.1 (11.9)	17.4 (16.0)	143.6 (.000)	1.318

^a Effect size, mean change in score divided by the standard deviation of mean baseline score

Table 5 Impact of current study treatment variables on satisfaction

During study treatment variables	DiabMedSat (week 26) (coefficient, <i>t</i> -ratio)			
	Overall***	Efficacy***	Symptoms***	Burden***
Intercept	76.720 (53.9)***	69.174 (37.9)***	80.670 (43.0)***	79.608 (46.4)***
Weight gain (final minus baseline, positive values = gain)	−0.218 (−8.9)***	−0.202 (−6.4)***	−0.341 (−10.5)***	−0.107 (−3.6)***
All minor hypoglycemic events during 4 weeks, final visit	−0.482 (−5.2)***	−0.415 (−3.5)***	−0.603 (−5.0)***	−0.402 (−3.6)***
Achieved physicians level of HbA1c (0 = No)	−2.453 (−1.7)	2.435 (1.3)	−5.203 (−2.8)**	−3.812 (−2.2)*
<i>F</i> -stat	37.585***	18.963***	48.909***	10.729***

* $P < 0.05$; ** $P < 0.01$, *** $P < 0.001$

previously suggested, factors that influence treatment satisfaction may vary depending upon the stage of treatment so that certain factors should be considered when starting a patient on a new treatment compared to once a patient has been on a treatment [16]. For example, age was shown to have a significant influence on satisfaction with treatment efficacy at study start, however, not after 26 weeks of treatment. Similarly, reaching HbA1c goal was significant after 26 weeks of treatment, but only when prior treatment variables were not taken into account. This suggests that assessing treatment satisfaction should be an ongoing part of a treatment plan in order to fully and currently understand how patients perceive their treatments.

When interpreting the influence of prior treatment factors, it is possible that response shift, the change in a person's perception or valuation of a concept over time [43] may explain, in part or in full, the finding that duration of disease was significantly related to increased overall satisfaction as well as with treatment efficacy and burden satisfaction. Patients having diabetes longer may accommodate and adapt to their disease and treatment over time thus finding diabetes less difficult to manage.

This study found that switching from a pretreatment oral medication to injectable insulin did not lower treatment satisfaction or increase treatment burden due to injectable insulin. In fact, patients previously on an oral treatment

alone had almost identical scores in satisfaction with amount of treatment burden at week 26 as those who had previously been on insulin (75.7 vs. 75.9) as well as a greater increase in overall treatment satisfaction than those previously on an insulin treatment alone (17.4 vs. 14.6). Additionally, the greatest improvement between oral and insulin was for the Efficacy domain (29.0 vs. 23.4). Efficacy has been shown to be a major driver in determining treatment satisfaction [2]. In the DiabMedSat, efficacy items include concepts of keeping blood sugar stable as well as impact on physical and emotional well-being suggesting that for patients, efficacy may be defined more broadly than just HbA1c levels.

When examining ongoing treatment factors that influence treatment satisfaction, it is clear that the occurrence of side effects is a major issue for patients and impacts treatment satisfaction overall as well as for each domain. In fact, the occurrence of side effects was more important than reaching HbA1c goal in determining treatment satisfaction. The influences of weight gain and major hypoglycemic events on treatment satisfaction have been previously shown [44]. The major influence of even minor hypoglycemic events is surprising and is suggestive that more research is needed to fully understand how and at what cost these minor hypoglycemic events have on treatment satisfaction and clinical outcomes.

It should be noted that there were 12 children (under age 18) included in the analyses and that the influence of the variables of interest on treatment satisfaction on children may differ from adults. Unfortunately, this sub-sample was too small to allow for any meaningful comparisons between children and adults. Also, unexamined in this study are potential differences in findings among countries, which should be examined in future research. Finally, we admit to certain limitations of observational studies which are in contrast to a controlled clinical trial design that examines treatment impact under highly structured and prescribed conditions. Although our data analysis set included about a third of the total global cohort (17,488/52,419, 33.3%), the demographic characteristics and outcomes were very much similar to those of the global cohort reported previously [31]. Other limitations of such studies have been discussed at some length previously and include factors such as the heterogeneity of healthcare systems across the participating countries, a lack of control groups for outcome comparison and the potential for patient recall bias during data collection [45]. The above factors also complicate the selection of predictor variables for regression analyses. However, given the large sample size, we do consider the analyses quite suggestive and clinically relevant. Observational data does not replace clinical trial data, but rather offers additional effectiveness information in a real-world setting to support clinical trial effectiveness

findings. Therefore, these findings may be more generalizable and relevant for a wide spectrum of clinician and treatment settings and provide greater insights into treatment satisfaction for the “average” person with diabetes. Additionally, the significant factors identified here which impact treatment satisfaction are most certainly not the only factors which have an effect, and further research is needed to identify these additional factors.

Conclusions

Patient treatment satisfaction can be a key factor influencing compliance and disease management in diabetes. This study found that patients who were treated with Biphasic Insulin Aspart 30 (NovoMix 30) reported improved treatment satisfaction after 26 weeks of treatment and that the improvement in treatment satisfaction was large enough to be considered clinically meaningful to patients. Factors that influence treatment satisfaction may vary depending upon the stage of treatment.

Acknowledgments This study was funded by Novo Nordisk.

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